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Opioids (natural and synthetic drugs with morphine-like actions) produce their primary toxic effects through an interaction with highly complex and integrated receptors in the central nervous system. This clinically results in miosis, altered mental status (ranging from clouding of consciousness to coma), and most importantly, ventilatory depression. The direct toxic effects of opiate drugs are readily reversible with the opioid antagonist naloxone. However, in the management of life-threatening opioid toxicity problems that frequently complicate an individual patient's management and hence require careful consideration and appropriate therapeutic intervention include: no intravenous access, incomplete response to the maximum dose to naloxone, and naloxone-induced opioid withdrawal syndrome.

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Life-threatening Opioid Toxicity

WILLIAM H. BICKELL, MD,* AND JOHN D. O'BENAR, PhD

Opioids (natural and synthetic drugs with morphine-like actions) produce their primary toxic effects through an interaction with highly complex and integrated receptors in the central nervous system. This clinically results in miosis, altered mental status (ranging from clouding of consciousness to coma), and most importantly, ventilatory depression. The direct toxic effects of opiate drugs are readily reversible with the opioid antagonist naloxone. However, in the management of life-threatening opioid toxicity problems that frequently complicate an individual patient's management and hence require careful consideration and appropriate therapeutic intervention include: no intravenous access, incomplete response to the maximum dose to naloxone, and naloxone-induced opioid withdrawal syndrome.

The term opium is derived from the Greek word meaning juice. The drug is derived from the juice of the poppy, Papaver somniferum. Opium contains over 20 alkaloids, including morphine and codeine. The term opioid was once used to designate drugs derived from opium (morphine, codeine, and many semisynthetic congeners of morphine). Opioid now refers to all drugs, natural and synthetic, with morphine-like actions.

Enormous quantities of opioids are prescribed on an outpatient basis as analgesics, antitussives, antidiarrheal agents, and for the treatment of opioid withdrawal. In addition, there are over 500,000 opioid addicts in the United States.[1] Despite the apparent prevalence of opioids in American society, overdoses are not common in areas where heroin addiction is not a problem. Nevertheless, opioid intoxications merit particular attention for three important reasons: (1) opioid overdoses are potentially life-threatening, causing death by acute ventilatory failure; (2) ventilatory failure is readily reversed with antidotal therapy; and (3) the management of opioid intoxication is frequently complicated with medicolegal problems. This chapter presents a discussion of life-threatening opioid intoxication and its management. The medical complications inherent with intravenous drug abuse endocarditis, pulmonary infections, and no cardiogenic pulmonary edema) are discussed elsewhere; hence this chapter will focus on opioid-induced acute ventilatory failure.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.

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OPIOID PHARMACOLOGY

Opiate drugs produce their pharmacologic effects through an interaction with highly

complex and integrated opioid receptors. The discovery of the first endogenous opioid receptor was in 1971.[2] Currently there is solid evidence for the existence of five major opioid receptors: mu, delta, kappa, epsilon, and sigma.[3] Although gamma, iota, and chi receptors have been proposed, further confirmation is currently underway.[4] The first three of these receptors have received the most study, and further divisions into isoreceptor subtypes have been made (ie, mu_1 and mu_2).[5] The physiologic role of a given receptor and its subtype is difficult to identify. Nonetheless, some tentative mechanisms have been discovered. The mu receptor has been determined to mediate analgesia and ventilatory depression. Furthermore, it has been determined that a subtype of the mu receptor, mu_1, mediates opioid-induced analgesia, whereas the mu_2 receptor mediates respiratory depression as well as morphine-induced bradycardia.[3,6-8] Moreover, mu_1 and the delta receptor have been shown to mediate opioid dependence.[9] The kappa receptor is responsible for opioid-induced dysphoria, sedation, and miosis.[8,9] The sigma receptor is currently the object of much attention. This receptor is postulated to mediate hallucinations, delusions, and dysphoric effects.[10] It is of particular interest that drugs such as ketamine and phencyclidine (PCP or "angel dust") appear to activate this receptor. Since it is believed that an endogenous ligand is also responsible for activating the sigma receptor, several groups are engaged in the search for the endogenous "angel dust" compound. As a result of their interaction with endogenous opioid receptors, opiate drugs are classified as agonists (meaning they promote or potentiate opioid receptor activity), antagonists (inhibit or block the activity of opioid receptors), and agonist–antagonists (dual effect of promoting the activity of some receptors while inhibiting the activity of others; Table 1).

Modulation of opioid receptor activity occurs through the action of several naturally occurring peptides that have properties similar to morphine. These compounds were first discovered in 1975, shortly after the discovery of opioid receptors, and were referred to as endogenous opioids. There are now three recognized classes of endogenous opioids: the enkephalins, the endorphins, and the dynorphins.[3] In addition to acting as ligands (or modulators) of the opioid receptors, these peptides have also been shown to function as neurotransmitters, hormones, and modulators of the immune system.[3,11] The body also manufactures certain anti-opioids or "endogenous-naloxone"-like compounds. Thyrotropin-releasing hormone and cholecystokinin almost certainly subserve this function.[12,13] Delta sleep-inducing peptide (DSIP) has also been implicated since it can precipitate opiate withdrawal.

Table 1. Classification of Opiate Drugs

- Opioid agonists
  - Natural opium derivatives
    - Morphine
    - Codeine
  - Semisynthetic opioids
    - Heroin
    - Hydromorphone (Dilaudid)
    - Oxymorphone (Numorphan)
    - Oxycodone (Percodan, Percocet)
  - Synthetic opioids
    - Meperidine (Demerol)
    - Methadone (Dolophine)
    - Levorphanol Tartrate (Levo-Dromoran)
    - Paregoric (Parepectolin, tincture of opium)
    - Piphenoxylate (Lomotil)
    - Fentanyl (Sublimaze)
    - Propoxyphene (Darvon)
- Pure opioid antagonists
  - Naloxone (Narcan)
  - Naltrexone (Trexan)
- Agonist–antagonists
  - Nalorphine (Nalline)
  - Levallorphan (Lortan)
  - Pentazocine (Talwin)
  - Butorphanol (Stadol)
  - Nubuphine (Nubain)
  - Cyclazocine
  - Propiram
  - Profadol

Table 2. Physiologic effects of opiate drugs

Organ	Effects
Central nervous system	Analgesia
	Miosis
	Dysphoria
	Emesis
	Mental clouding
	Ventilatory depression (coma, ventilatory failure)
Cardiovascular system	Increased venous capacitance (orthostatic hypotension)
Gastrointestinal system	
Stomach	Decreased gastric motility
	Decreased HCl secretion
	Increased antral tone (delayed gastric emptying)
Large and small intestine	Decreased propulsive contrations
	Increased resting tone of the illocecal valve and anal sphincter (constipation, fecal impaction)
Lung	Histamine release
	Increased bronchial tone (bronchospasm)
Genitourinary system	Increased detrussor tone (urinary retention)
Skin	Vasodilitation
	Histamine release (urticaria, puritis)

The following information should help elucidate this complex system. The distinction among opioid receptor subtypes is not rigid, since multiple receptor subtypes can mediate the same response; furthermore, the same receptor can mediate multiple responses; moreover, it has even been proposed that transformation of one receptor type into another may occur.[14,15]

CLINICAL MANIFESTATIONS OF OPIOIDS

Opioids produce their major effect on the central nervous system with minor effects on the cardiovascular, gastrointestinal, and genitourinary system (Table 2).[2] The primary toxic manifestation of opioids is mediated by their activity at the mu and kappa receptors in the central nervous system. This, in turn, results in altered mental status (ranging from clouding of consciousness to coma) and, most importantly, ventilatory depression. Opioid-induced ventilatory depression occurs as a result of complex interactions with the central and peripheral mediators of ventilation.[16] The areas of the medulla that control breathing (nucleus tractus solitarius and nucleus ambiguus) are richly supplied with mu receptors.[17] Ventilatory depression primarily involves a decrease in tidal volume.[18] Respiratory frequency is not affected until a much larger dose of the drug is received.[19] As a result, the early stages of ventilatory failure are characterized by shallow respirations with normal frequency. Respiratory rate is therefore an unreliable measure of ventilation following opioid overdose. The reduction in ventilation is accompanied by a decreased chemosensitivity to carbon dioxide.[20] The carotid body is particularly well endowed with mu receptors; hence, ventilatory responses to hypoxemia are depressed by opiate drugs to an even greater magnitude than responses to hypercapnia.[21] This accounts for why many elderly patients and those with chronic obstructive pulmonary disease are especially sensitive to the ventilatory depressant effects of opiate drugs.

The classical manifestation of opioid intoxication is the triad of unconsciousness, miotic pupils, and shallow infrequent

breathing. However, life-threatening opioid toxicity does not always present in this manner. For example, mydriasis rather than miosis can occur as a result of a mixed overdose (eg, tricyclic antidepressants), prolonged hypoxemia, or may occur following a meperidine overdose. Furthermore, ventilatory depression can occur in the responsive patient. (These patients can be instructed to breathe at a depth and frequency necessary for adequate ventilation.) Moreover, as discussed previously, opioid-induced ventilatory failure can occur in the face of a normal respiratory rate. Other manifestations of intravenous substance abuse (ie, cutaneous needle marks, abscesses, cellulitis) may be evident and direct the physician's attention to the correct diagnosis. Pink frothy sputum is seen occasionally as a result of opioid-induced noncardiogenic pulmonary edema.

MANAGEMENT OF LIFE-THREATENING OPIOID TOXICITY

With very few exceptions, the cause of death following an opioid overdose is acute ventilatory failure. This problem can be readily managed with ventilatory assistance. Furthermore, all central nervous system and ventilatory depressant effects are completely reversible with naloxone; hence, all deaths from acute opioid overdose are avoidable theoretically. Therefore, the primary concern is the patients' ventilatory status. In patients with a respiratory rate less than 8/min or exhibiting cyanosis, ventilatory assistance must be instituted immediately. Intravenous access may then be established and the patient given naloxone to reverse the central nervous system depressant effects of the opioid.

Naloxone Administration

Naloxone is the drug of choice for the treatment of opioid toxicity. Naloxone is a pure antagonist, meaning it has no pharmacologic activity other than displacing opiate drugs from the opioid receptor. Although the dose of naloxone required for pharmacologic reversal is a function of the opiate drug concentration and receptor affinity, some general guidelines can be established. The intravenous dose of naloxone recommended for unconscious or obtunded patients without ventilatory depression is 0.4–0.8 mg. Occasionally this is insufficient to reverse the given opioid effect, particularly in patients who have ingested large quantities of codeine, synthetic opioids, and mixed agonist-antagonists (Table 3).[1] Therefore, if the altered mental status is not reversed in 3 to 4 minutes, 2 mg intravenous naloxone should be given and repeated, if necessary, up to a total of 20 mg.[1] In patients with ventilatory depression, the initial intravenous dose of naloxone should be 2 mg to insure a prompt and complete reversal. If a complete response is not seen within 3 to 4 minutes, 2 mg boluses of naloxone should be given every 4 minutes until (1) reversal of both coma and ventilatory depression is accomplished, or (2) a total of 20 mg of naloxone has been administered (after which it can confidently be assumed that the primary problem is not mediated through the opioid receptors).

Table 3. Opioids that Require Larger Doses of Naloxone to Reverse Central System/ Ventilatory Depression

Natural opium derivatives
Codeine
Synthetic opiates
Diphenoxylate (active ingredient in Lomotil)
Propoxyphene (Darvon)
Mixed opioid agonist–antagonists
Pentazocine (Talwin)
Butorphanol (Stadol)
Nalbuphine (Nubain)

One of the more frequent problems following successful naloxone therapy is the false sense that the problem has been both diagnosed and "cured." Clinicians inexperienced in the use of naloxone will leave the patient unattended, only to discover him/her 30 minutes later in the same clinical con-

dition as before treatment. With the exception of fentanyl, the half-life of naloxone is less than that of all the other opiate drugs, thus after 20 to 30 minutes the toxic opioid effects generally reappear.[2] Therefore, close observation and further naloxone therapy is required.

There are two accepted methods for the continued administration of naloxone: (1) continuous infusion, and (2) rebolus.[1] For the former method, the amount of naloxone necessary to reverse central nervous system and ventilatory depression is given hourly in a continuous intravenous infusion. For example, if 4 mg naloxone was required to restore adequate ventilation and central nervous system responsiveness, then 4 mg/hr should be given as a continuous intravenous infusion. Because the plasma level of naloxone frequently declines before the continuous infusion takes over, it may be necessary to administer one-half the initial loading dose at 30 minutes. Furthermore, it may be necessary to increase the infusion rate if depression of ventilation or the level of consciousness reoccurs. The rebolus technique is reserved for patients with no opioid-induced ventilatory depression, and those patients too agitated to be safely managed with a continuous intravenous infusion. Under these circumstances, naloxone can be given every 15–30 minutes through a well-secured heparin lock or as an hourly intramuscular injection.

CLINICAL PROBLEMS IN OPIOID OVERDOSE MANAGEMENT

Although the diagnosis and treatment of opiate drug overdose may appear to be straightforward, problems frequently occur that can complicate an individual patient's management.

Opioid-induced Ventilatory Depression in a Patient with no Peripheral Intravenous Access

Intravenous substance abusers are notorious for their paucity of peripheral veins. Heroin addicts will go to extraordinary means to obtain venous access. For example, self-administered internal jugular vein injections (pocket shooting) is commonly employed in those who have lost peripheral venous access because of repeated intravenous injections. Fortunately there are several alternative routes of naloxone administration: subcutaneous, intramuscular, and sublingual. Moreover, the drug is readily absorbed following endotracheal administration. In the case of an obvious opioid overdose, many clinicians elect to manage ventilatory depression with bag–valve–mask assisted ventilation while waiting 3–4 minutes for naloxone to reverse this problem. However, when intravenous access is not readily available, intramuscular or subcutaneous routes of naloxone administration require up to 30 minutes for the pharmacologic reversal of ventilatory depression. (Sublingual injection into the muscular vascular floor of the subglossal fossa avoiding muscularis of tongue may give onset of action within seconds.[22]) Bag–valve–mask ventilation for this length of time is hazardous because of the problems inherent with the prolonged technique (ie, gastric distension, aspiration, and inadequate ventilation). When intravenous access is not readily available, therefore, endotracheal intubation should be accomplished expeditiously. Naloxone can then be given down the endotracheal tube. (The anticipated time to reversal of opioid toxicity is very close to that achieved with intravenous naloxone.) Under controlled conditions venous cannulation can be reattempted or, alternatively, the patient can be managed with hourly intramuscular naloxone injections. Attempting central venous access is both unnecessary and potentially hazardous during the resuscitative phase of the patient's management.

Partial or Incomplete Response to the Maximum Dose of Naloxone

Naloxone may produce a definite but incomplete response. For example, naloxone

administration may restore adequate ventilation, yet the patient's altered mental status remains unaffected. If this condition persists after administration of 20 mg of naloxone, the problem is beyond the direct pharmacologic effects of an opioid.

An incomplete naloxone response frequently results from a complication of opioid intoxication, the most common of which is hypoxia (Table 4). This occurs following prolonged ventilatory failure, aspiration, or opioid-induced pulmonary edema. Moreover, hypoxia or the direct effect of an opiate drug may result in a generalized tonic clonic seizure, hence the physician may witness a postictal condition.

An incomplete naloxone response can also result from a concomitant medical problem (Table 4). Over 90% of all opioid intoxications are mixed with other agents.[1] Although the majority of these are inconsequential, an additional agent will occasionally be present in a quantity sufficient to produce central nervous system depression. (This occurs most commonly with ethanol, barbiturates, or benzodiazepines.) Head trauma is an often overlooked yet critical consideration in opiate drug overdose patients. Any suspicion or evidence of this problem on history or examination is an indication for immediate computed tomography scan of the head. Hypothermia is another important consideration in the patient with an incomplete naloxone response. This problem occurs following environmental exposure in patients with opioid-induced altered mental status. Hypothermia also results from the "street" practice of attempting to stimulate the heroin overdose victim with an ice bath. Hypoglycemia is encountered in up to 5% of the opioid overdoses, and in selected cases may be severe enough to result in altered mental status.[23] This problem is not directly related to the opiate drug itself but rather to an associated ingestion of another substance (ie, ethanol) or to other underlying medical conditions.

In communities with a large population of heroin addicts, the clinical problem of an incomplete naloxone response is not uncommon. From the foregoing discussion it is easily appreciated that this problem is often secondary to potentially life-threatening, yet treatable, conditions. Therefore, patients with a partial response following the maximum dose of naloxone should be evaluated aggressively. At the very minimum this should include a thorough physical examination, chest radiograph, arterial blood gas, serum glucose and electrolytes, with further consideration of computed tomography scanning and toxicologic laboratory analysis if indicated.

Table 4. Causes of an Incomplete Response to Naloxone

Direct complication of the opioid
Anoxic encephalopathy
Persistent hypoxemia resulting from aspiration or pulmonary edema
Postictal state
Concomitant medical problem
Mixed overdose of opioid and another agent producing central nervous system depression
Head trauma
Hypothermia
Hypoglycemia

Naloxone Therapy Precipitates the Opioid Withdrawal Syndrome

The withdrawal syndrome is a well-publicized complication of opioid addiction. Although opioid withdrawal is rarely, if ever life-threatening, it is distressing to both the patient and physician. Following abstinence in the individual with physical opioid dependence, a predictable sequence of symptoms occur.[1,24] The early phase of withdrawal is manifested by anxiety, lacrimation, rhinorrhea, and frequent yawning. In the later stages, nausea, vomiting, and diarrhea occur in conjunction with moderate elevations in blood pressure, pulse, and temperature. Although the sequence of symptoms is virtually the same for all opioids, the timing is directly

Table 5. Withdrawal Symptoms Following Heroin Abstinence

Onset (hours)	Symptoms
4–6	Anxiety Yawning Lacrimation Diaphoresis Rhinorrhea
12–18	Mydriasis Piloerection Fasciculations Myalgias Hyperpyrexia Tachycardia Mild hypertension
>24	Nausea Vomiting Diarrhea Insomnia

related to the duration of action of the drug. For agents such as heroin, with rapid onset and brief duration of action, withdrawal begins within 4–6 hours of abstinence (Table 5). Conversely, for agents such as methadone, with delayed onset and prolonged duration of action, withdrawal is not seen for up to 48 hours. Naloxone in sufficient doses will abruptly precipitate the withdrawal syndrome in patients with physical opioid dependence. As a result it is recommended that addicts with opioid-induced coma be given no more than 0.2 mg naloxone every 5 minutes until consciousness is regained.[1] However, in patients with ventilatory depression the time required to titrate reversal without precipitating withdrawal is excessive. Therefore, 2 mg is the recommended starting dose in those with opioid-induced ventilatory depression. If withdrawal symptoms occur following this dose, the patient can be treated symptomatically with oral clonidine and the rate of the continuous naloxone infusion adjusted to minimize these symptoms without compromising ventilation or the level of consciousness. Naloxone should never be withheld because of the concern that opioid withdrawal may occur.

A Patient with Coma and Ventilatory Depression Responds to Naloxone and Demands Immediate Release from the Hospital

This is a frequent problem for emergency departments managing a large number of heroin addicts. As discussed earlier, the utilization of naloxone for the reversal of central nervous system and ventilatory depression may precipitate withdrawal. As a result patients will often demand release from the hospital for the purpose of administering more opioid. In the case of an accidental (nonsuicidal) overdose, this poses a difficult medicolegal problem. Due to the relatively short half-life of naloxone, ventilatory depression will probably reappear. Therefore, all efforts must be made to retain these patients for appropriate treatment. Family, friends, social workers, or possibly the clergy are helpful in this endeavor. Patients who persist in their decision to refuse treatment and leave the hospital should be retained if, in the judgement of the attending physician, naloxone is necessary for the patient's well-being.[25] This action must be done in a caring, compassionate manner with the minimal amount of force necessary, and in accordance with local hospital policy.

CONSIDERATIONS FOLLOWING ORAL OPIATE DRUG INGESTIONS

The resuscitative management of obtunded patients with ventilatory compromise is the same regardless of the route of opioid administration. Because of the increase in antral tone and the reduction in intestinal peristalsis, gastric emptying is indicated regardless of the time that has passed since ingestion. Opioids are readily absorbed by activated charcoal; hence, the usual steps of administering 30–60 g activated charcoal with a cathartic are indicated. An opioid-

mediated delay in gastrointestinal transit time may occur despite naloxone reversal of central nervous system depression. Therefore, if charcoal stools are not produced within 4 hours, an increase in the rate of naloxone infusion may be required to improve intestinal peristalsis. Methadone is the most common cause of oral opioid overdose resulting in ventilatory depression. This problem is particularly prevalent in communities with heavily utilized methadone maintenance programs. Symptoms generally begin within 4 hours of ingestion, however, ventilatory depression may not occur for up to 8 hours. Although these patients respond readily to naloxone, its continued infusion may be required for 36 hours or more.

AGENTS OTHER THAN NALOXONE USED TO REVERSE OPIOID TOXICITY

Nalorphine was one of the first opioid antagonists used. This drug is capable of reversing the central nervous system depressant effects of morphine-like substances. In large doses, however, nalorphine itself produces analgesia, dysphoric effects, and ventilatory depression. This dual property results from the combined agonist–antagonist pharmacologic action at the opioid receptor. Following its clinical availability, naloxone, the pure antagonist, has become the drug of choice for the management of opioid toxicity. Naltrexone is a new medication of the pure opioid antagonist class. It is now available in the oral form and is used exclusively to assist individuals in abstaining from heroin or other opiate drugs. Naltrexone currently has no role in the acute management of opioid overdose. Nevertheless, in those patients with no evidence of withdrawal following naloxone bolusing, a long-acting antagonist such as naltrexone may prove beneficial in preventing opioid toxicity from reappearing.

IN-HOSPITAL MANAGEMENT

It has been our practice to admit all patients with opioid-induced ventilatory depression to the intensive care unit for continuous naloxone infusion and close observation. After 8–10 hours the naloxone infusion is stopped and the patient is closely observed free of opioid antagonist. The assessment for the reappearance of opiate drug toxicity is made no earlier than 1 hour after the naloxone infusion is stopped. Those patients who have ingested long-acting opioids such as methadone, or are having delayed absorption due to enteric pill concretions or decreased intestinal peristalsis, frequently require reinstitution of the naloxone infusion.

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